REMARKS

The claims have been amended such that the cancer is limited to breast cancer and the organism is a human. Support for these amendments can be found, *inter alia*, in cancelled Claims 36 and 38.

Also, in Claims 28(b) and 29(b) and (d), "immobilized on a solid support" has been amended to recite "carried out on a solid support", and Claim 19(f) has been replaced with:

> "(f) preparing at least one solid support carrying the resulting isolated selected mRNA species or isolated cDNA species of step (e) so as to form a gene transcript pattern probe kit."

Support for these amendments can be found at page 19, line 10, of the present specification. Also, at page 18, lines 4-6, the use of multiple wells as a solid support is described.

The methods of the present invention can be performed using probes that are not actually immobilized on a solid support, but are simply carried by a solid support. For example, the probes may be spotted onto a 386-well plate, and the wells subsequently created around the probes. Reagents are then added to each well and a real-time RT-PCR reaction can be carried out to quantify the level of hybridization to the probes. In this respect, the probes are held in place by the well, but they are not attached to the support in any way.

Hence, the amendments to the claims do not constitute new matter, and thus entry is respectfully requested.

In paragraph 3, on page 2 of the Office Action, the Examiner requests that Applicants update the status of the parent application in the first paragraph of the specification.

Accordingly, Applicants hereby amend the specification as requested by the Examiner to indicate that the parent application, i.e., U.S. Application No. 09/429,003, has now issued as U.S. Patent 6,720,138.

In paragraph 5, on page 2 of the Office Action, the Examiner rejects Claims 28 and 30-38 under 38 U.S.C. § 112, second paragraph.

Specifically, the Examiner states that the recitation "said cancer" in step (a) lacks proper antecedent basis, because Claim 28 does not previously recite an organism that has any cancer.

In view of the amendment to Claim 28, Applicants respectfully submit that the claims clearly and definitely recite the invention of interest, and thus, Applicants request withdrawal of the Examiner's rejection.

In paragraph 7, on page 3 of the Office Action, the Examiner rejects Claims 18-38 under 35 U.S.C. § 112, first paragraph.

Specifically, the Examiner states that there is no support in the specification for the limitation that the mRNA is isolated from blood cells from a patient having cancer, wherein said cells (which are from blood) "have not contacted the area of said cancer".

In addition, in paragraph 8, on page 4 of the Office Action, the Examiner rejects Claims 18-38 under 35 U.S.C. §112, first paragraph.

Specifically, on page 7 of the Office Action, the Examiner states that the specification does not provide any guidance on how to identify blood cells within a blood sample that have not come into contact with a particular part of the body.

For the following reasons, Applicants respectfully traverse the Examiner's rejections.

The Examiner is requested to note that the claims have been limited to "breast cancer" and "humans"; and also have been limited to breast cancer in humans without reference to the stage of the cancer; and further have been limited to using blood from "more than one" humans, thereby rendering moot this aspect of the Examiner's rejection.

The specification contains reference to using blood samples for cancer detection at page 6, second paragraph; and page 7, 3 lines from the bottom and page 23, lines 8 and 19. Regarding the "not contacted the area of said cancer" language, Example 1 discloses the use of a blood sample for the diagnosis of Alzheimer syndrome. Peripheral blood withdrawn from a patient for this purpose will inherently not have contacted the site of disease as it will not have crossed the blood-brain barrier. Thus, the specification does not contemplate using blood samples where the blood cells have not contacted the site of disease.

In addition, the penultimate paragraph of page 10 of the present specification refers to the whole organism responding to the condition, and page 23, second full paragraph, refers to effects being observed on body parts distant from the site of interest. Also, page 11, third full paragraph, contains reference to early diagnosis before other symptoms appear. Early diagnosis of tumorous cancer would mean that the tumor would still be *in situ*, i.e., the tumor has not yet penetrated the basement membrane of the blood vessel. Thus, the circulating blood cells would not have come into contact with the tumor.

The enclosed references (Cady, *Cancer*, 65:634-647 (1990); Ikeda et al, *Radiology*, 172:661-666 (1989); and Rebner et al,

Radiology, 190:623-631 (1994)) show that it was known in the art as of Applicants' priority date to isolate blood that has not come into contact with a breast cancer. As mentioned briefly above, the accepted medical term *in situ* is used to describe breast cancer tumours that have not yet extended beyond the basement membrane into the surrounding stoma, i.e., they have not penetrated into the circulatory system. The blood would inherently not have contacted the area of disease. Cady illustrates that patients having ductal carcinoma *in situ* (DCIS) can be identified by mammographs (page 637, column 2, penultimate paragraph), i.e., patients having breast cancer in which the blood has not contacted the site of disease can be identified by those skilled in the art.

The enclosed details and experimental data provided in Appendix A attached hereto demonstrate that the present invention is effective to diagnose DCIS and IDC (stage I cancer). Briefly, the experiment was conducted on whole blood from 48 females, 20 with breast cancer, 20 healthy controls and 8 with colon cancer. Of the 20 females with breast cancer, 10 had stage 0 and 10 had stage I cancer. Total RNA was extracted and hybridized to high density arrays and the amount of hybridization to the arrays was measured. The results were analyzed to identify differentially expressed genes between the sample groups. Several genes were identified as informative. The diagnosis ability of the informative probes were determined by cross-validation. Correct prediction of sample diseased or healthy status was achieved in three of the groups and only a small number of samples were incorrectly predicted in the fourth group. The conclusion was that cancer samples can readily be discriminated from normal samples using the identified probes, and that blood from DCIS (stage 0) cancers that had not come

into contact with the site of the disease could be used to predict the correct status of the sample.

Accordingly, Applicants respectfully submit that the claims clearly have written description support in the specification and are enabled by the present specification. Thus, Applicants request withdrawal of the Examiner's rejections.

In paragraph 9, on page 13 of the Office Action, the Examiner rejects Claims 27-38 under 35 U.S.C. § 112, first paragraph, as lacking written description.

Specifically, the Examiner states that these claims are directed to a particular set of probes that are identified only by their function, i.e., that they are differentially expressed in two samples, and they are indicative of cancer, and by the type of cells that they were identified within (i.e., blood cells that have not touched the area of disease and that were isolated at a distance from the area of disease). Further, the Examiner states that the specification and claims suggest that there are hundreds of possible genes that meet these requirements and that the specification does not provide support for even a single example of an appropriate mRNA or cDNA probe for use in the claimed methods. Hence, the Examiner concludes that while the specification suggests that such molecules might exist, the specification does not provide any written description of what the structure of these molecules is, and thus the claims lack written description.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The claims have been limited to humans and breast cancer, thereby significantly reducing the total number of genes from which to choose. It is submitted that the claims limited to

breast cancer in humans, without reference to the stage of the cancer, are supported by the specification and can be carried out by one skilled in the art using the teaching in the specification.

Accordingly, Applicants respectfully submit that the claims clearly have written description support in the specification, and thus, Applicants request withdrawal of the Examiner's rejection.

In paragraph 11, on page 15 of the Office Action, the Examiner provisionally rejects Claims 15-38 under the doctrine of obviousness-type double-patenting as being unpatentable over Claims 1-36 of co-pending application, Serial No. 11/149,370.

As this rejection is provisional in nature, i.e., the co-pending application has not yet issued into a patent, this rejection is traversed on that basis, i.e., if the remaining rejections are overcome, the Examiner is required to issue the present application, assuming that the co-pending application has not previously issued into a patent.

In view of the amendments to the Claims and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at the below-listed number on any matters which might arise.

Respectfully submitted,

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Date: February 8, 2007